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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,235	07/22/2004	Malgorzata Anna Kisielow	1-32330A/FMI	9191

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	

ART UNIT	PAPER NUMBER
1633	

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02/20/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/502,235	KISIELOW ET AL.	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *13 and 21-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 14-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Status

Applicant's response of December 3, 2007, to the non-final action dated June 1, 2007 has been entered. No claims were amended, canceled or newly added. Claims 1-23 are currently pending in the application. Claims 13 and 21-23 remain withdrawn from consideration, without traverse, as drawn to non-elected inventions. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

Claims 1-12, and 14-20 are under current examination.

Response to Claim Rejections - 35 USC § 112- Second Paragraph

Claims 1-12 and 14-20 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite. The previous action dated June 1, 2007 erroneously included claim 20 in the rejection, as dependent from claim 1. Accordingly, the rejection of claim 20 is hereby withdrawn. The rejection set forth on p.2 of the previous office action dated June 1, 2007 is maintained for claims 1-12 and 14-19, for reasons of record.

The previous rejection stated: "Step (a) of claim 1 recites: "determining from a gene product of interest, a specific isoform of interest from said gene product". As said determination requires a plurality of gene products, it is not clear how a single gene product may lead one to the various isoforms. The determination can be made from all the products of a gene of interest." Applicants contend that there is confusion over the meaning of the "determination step", and attempt to add some clarification. Applicants agree that "the determination [of an isoform of interest] can be made from all the products of a gene of interest." Applicants further state: "It is not the single gene product itself that leads to one of the various isoforms, but knowledge of the single gene product that leads to one of the isoforms (i.e., the isoform of interest). So as to eliminate any potential confusion, the "determination step" presupposes of the practitioner (i) knowledge of a gene product of interest (e.g., the ShcA gene product, as encoded by the ShcA

gene, in Example 1); and (ii) knowledge of an isoform of interest (e.g., the p66ShcA isoform, in the Examples). The determination is made possible by knowledge on the part of the practitioner."

Applicants' arguments have been fully considered, but are not found persuasive. In response, it should be noted that the clarification provided with respect to Applicants' invention is not remedial to the claim language at issue, that forms the basis of the rejection. The preamble for the method of claim 1 is directed to expression of a specific isoform of a gene product, absent other isoforms of said gene product. However, a gene expressing several isoforms cannot have a single gene product (as recited in the preamble and step (a)), but must necessarily have a number of gene products or isoforms. As only a specific isoform is of interest, "a gene product" as recited in step (a) of claim 1, comprising all the isoforms would not be of interest. The claim should be amended so as to clarify the discrepancy between gene product and isoform of interest.

Therefore, the rejection of claims 1-12 and 14-19 is maintained for reasons of record, and the foregoing commentary.

Response to Claim Rejections - 35 USC § 112, Written Description

Claims 1-12 and 14-20 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The rejection set forth on pp. 3-5 of the previous office action dated June 1, 2007 is maintained for claims 1-12 and 14-20, for reasons of record.

Applicants disagree with the rejection, stating: "Applicants feel the first part of the Examiner's statement on page 3, line 5 of the second paragraph to be in error ("Additionally arguing, that the products themselves (e.g., the encoded proteins) are not essential to the claimed methods of the invention..."). This is not the case. The products themselves are essential to the claimed methods, but it is those precise gene products of interest to the practitioner, versus the plenary set of all gene products which are capable of being expressed by more than one isoform. The latter is not essential, which is why the present claim set need not be commensurately broad with that plenary set (in terms of written description or enablement)." Applicants' arguments have been fully considered, but are not found persuasive.

In response, it is noted that the Examiner's statement Applicants are referring to was quoted from Applicants' own arguments presented in the amendment dated April 10, 2007, wherein on page 7 Applicants stated: "Applicants reiterate their past arguments, including that the gene products themselves (e.g. the encoded proteins) are not essential to the claimed methods of the invention". In direct contradiction, Applicants now state: "The products themselves are essential to the claimed methods". Moreover, Applicants' statement: "the plenary set of all gene products which are capable of being expressed by more than one isoform" is non sequitur, because an isoform is necessarily a single gene expression product and is incapable of expressing a plenary set of all gene products.

Applicants further argue that there is nothing special about a mutant isoform or a tumor suppressive mutant isoform such that the ShcA example given in the present specification would be an insufficient exemplification. In both the case of signaling adaptor/scaffold gene products and mutant/tumor suppressive mutant gene products, there can exist isoforms whose identities can be easily determined by a person of ordinary skill in the art. The knowledge of said isoforms that is a prerequisite of practicing the invention (especially with the addition of the "determining step") is exactly the same; therefore, the Examples of the present specification is sufficient, without additional need for an example concerning mutant/tumor suppressive mutant gene products and their isoforms.

Such is not found persuasive, because, as previously indicated, the issue is one of possession by Applicants at the time of the instant invention. The instant claims require knowledge of all the isoforms of any gene from any of numerous species of animals or plants, including those yet to be discovered. Applicants' single example for the shcA gene is not an adequate representation of the genus of isoforms of any mammalian gene to satisfy the written description requirement.

Applicants additionally argue that if the practitioner already knows her gene of interest and isoform of interest (as well as the isoforms not of interest that she wishes to knock down), then there is no need to learn the same from the present specification.

Such is not found persuasive because knowledge of all the isoforms of any gene of interest (as instantly claimed) was not generally available to either Applicants, or a person of skill in the art at the time of invention, and as previously indicated, the instantly claimed method of expressing a specific isoform of any mammalian gene product, in any cell, absent other isoforms of said gene product, comprises introducing into said cell a ds RNA having at least 95% sequence identity to a common nucleic acid sequence shared by two or more isoforms of said gene product. As such (and as stated by Applicants in the foregoing), the claims require specific knowledge of the sequences for the desired isoforms of any gene product of interest, whether endogenous to said cell or isoforms that may be exogenous in origin, to determine the nature of the sequences that would constitute a common and shared nucleic acid. The specification defines isoform "to encompass gene products that are produced as a result of differential gene splicing as well as from the use of alternative transcription start sites. In addition, …the term isoforms include any closely related sequences and therefore may include a mutated gene in a cell" (p. 10, lines 30-31, bridging p. 11, lines 1-4). The specification discloses only the Shc gene family as exemplary for isoforms of a signaling adaptor/scaffold gene product (Example 1, p. 17) with ShcA, as exemplary for the desired isoform (line 6, p.18) and specifically describe the use of 21-mer oligonucleotide pairs as siRNAs of Shc (lines 28-29, p. 18). However, the specification provides no description of the substantial number of genes that can express more than one isoform, or have closely related sequences thereto, in any cell, as claimed. The specification is further devoid of any description for a desired isoform replacing a mutant isoform or a tumor suppressive mutant isoform in a cell.

The method of the instant invention requires and is dependent on RNA interference by double stranded ribonucleic acid, that must be designed in a sequence specific manner, to form a specific secondary structure, and empirically tested to determine whether any particular double stranded sequence having 95% sequence identity to a sequence commonly shared by the different isoforms would result in proper suppression of expression of all said isoforms. The instant claims are directed to expressing a specific isoform of any gene product, whereas the limited information provided by the specification is for the Shc family and the design of a siRNA, only applicable to the Shc genes. Applicants have acknowledged that a skilled

practitioner may utilize the instantly claimed method, when knowledge regarding the gene of interest, the isoforms and the sequences encoded thereby is already possessed. However, such knowledge is in fact absent from the instant specification, except with regards to the Shc gene. The method of the instant invention further requires the suppression of expression of numerous isoforms of a multitude of genes by at least one siRNA molecule and said suppression would require specific knowledge of shared sequences among the different isoforms of a gene. The instant claims embrace the sequences for the isoforms of a genus of any gene, thus encompassing substantial sequence variation within the genus.

Thus, the rejection of claims 1-12 and 14-20, is maintained for reasons of record and the foregoing discussion.

Response to Claim Rejections - 35 USC § 112-Lack of Enablement

Claim 1-12 and 14-20 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The rejection set forth on pp. 8-11 of the previous office action dated June 1, 2007 is maintained for claims 1-12 and 14-20, for reasons of record.

Applicants disagree, arguing that contrary to the Examiner's assertion in the previous office action, the present invention does not require "the complete suppression of expression of all isoforms, variants, mutants, etc." because as seen throughout the present specification, isoforms not of interest are knocked down relative to those of interest, although not necessarily fully. For example, the present published specification employ language to describe the expression of non-desired isoforms such as "almost completely"; and "very low." Applicants conclude that for this reason, the enablement standard is lower than described by the Examiner, and is met by the present specification for the present claims. Applicants' arguments have been fully considered, but are not found persuasive.

In response, Applicants are directed to the language of the instant claims, requiring "expressing a specific isoform of a gene product in a mammalian cell absent other isoforms of said gene product". Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26

USPQ2d 1057 (Fed. Cir. 1993). It should further be noted that had the claims required a significant attenuation of expression for the undesired isoforms, instead of their complete absence, the grounds for rejection of the claims would still remain.

Applicants further argue, there is nothing about the shcA gene product that would suggest it is easier or more difficult than other proteins in terms of the capacity of its isoforms to be selectively knocked down. Stating: "One of the ways in which an isoform of interest (of a gene product of interest) become "of interest" to an ordinarily skilled practitioner is through a recognition that said isoform is capable of isolation, e.g., through the administration of RNAi. This can be easily determined scientifically, without undue experimentation."

Such is not found persuasive, because the post-filing art of record clearly suggests that administering dsRNA, either *in vitro* or *in vivo*, to attenuate expression of target genes is not a reproducible or predictable art.

The unpredictability of attenuating expression of a target gene in all types of cells, including mammalian cells, by RNA interference (RNAi) is evident in prior and post-filing art. While it is recognized that introduction of dsRNA that is targeted to a specific gene may result in attenuation of expression of the targeted gene, the degree of attenuation and the length of time that attenuation is achieved is not predictable. Caplen et al. (Gene, 252:95-105, 2000; of record) provide evidence of the unpredictability of dsRNA attenuation of a targeted gene in vertebrate cells *in vitro*. Caplen et al. report that although dsRNA inhibits gene expression in cultured *Drosophila* cells, screening of three commonly used cell lines from three different species: human, hamster, and mouse, using cells expressing transgenes both transiently and permanently, produced mixed results.

Given these teachings, the skilled artisan would not know *a priori* whether introduction of dsRNA or hairpin nucleic acids into any type of cell, would result in successful attenuation/inhibition of a target gene. In fact, the prior art teaches that successful delivery of nucleotide sequences to a target cell *in vitro*, such that the oligonucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically.

The specification does not provide the guidance required to overcome the art-recognized unpredictability of dsRNA for use in RNA interference in various types of cells. Therefore, in view of the lack of teachings or guidance provided by the specification with regard to expression

restricted to only one specific isoform product of any gene having multiple isoforms, in any cell type, and for the specific reasons cited above, it would have required undue experimentation for an Artisan of skill to make and use the claimed invention.

Thus, the rejection of claims 1-12 and 14-20, is maintained for reasons of record and the foregoing discussion.

Response to Claim Rejections - 35 USC § 101-Lack of Utility

Claims 1-12 and 14-20 stand rejected under 35 U.S.C.§ 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility. The rejection set forth on pp. 6-8 of the previous office action dated June 1, 2007 is maintained for claims 1-12 and 14-20, for reasons of record.

Applicants disagree, arguing the present methods do not require further research in order to fully realize their utility, because, they possess a present utility, and enable further research in the field of molecular biology and therapeutic treatment of diseases, among others. Further arguing: "In the same way that the present Examples show how signaling adaptor/scaffold gene products such as ShcA can be studied in a substantial and meaningful way by the present invention, the present claims extend those findings to a wide variety of gene products." Applicants' arguments have been fully considered, but are not found persuasive.

The instantly claimed method provides a means to test and evaluate RNAi approaches and to study a specific isoform product of a gene, in the absence of other "interfering" isoforms. Applicants had previously stated on the record: "The present claims, in their amended state, describe *in vitro* analytical techniques best suited for the study of certain desired isoforms of gene products of interest". Applicants have again admitted that the method of the instant invention allows the study of gene products for further research in the field of molecular biology and disease treatment.

Therefore, the foregoing constitutes using the invention as an object of research in order to determine the function or effects of a specific isoform of interest, or to evaluate dsRNA inhibition, and does not meet the requirement for a substantial utility. As indicated in the utility

guidelines, utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. As the instantly claimed method lacks a substantial utility, the invention further lacks a well established utility.

Thus, the rejection of claims 1-12 and 14-20, is maintained for reasons of record and the foregoing discussion.

Response to Claim Rejections - 35 USC § 102

Claims 1-12 and 14-20 stand rejected under 35 USC § 102(e), as anticipated by Tuschl et al. (U. S. Patent Application No.: 2004/0259247, filed Nov. 29, 2001). The rejection set forth on pp. 8-10 of the office action dated October 10, 2006, and pp. 11-12 of the previous office action dated June 1, 2007 is maintained for claims 1-12 and 14-20, for reasons of record.

Applicants disagree with the rejection, stating that the Tuschl reference lacks the all-important "determination step" requiring of the practitioner (i) knowledge of a gene product of interest and (ii) knowledge of an isoform of interest. As the purpose of the Tuschl methods is to knock down a gene of interest for therapeutic purposes, irrespective of the presence of multiple isoforms, said determination step is meaningless and not employed. Applicants' arguments have been fully considered, but are not found persuasive.

As previously indicated, the invention of Tuschl et al. utilizes double stranded RNA (siRNA) for RNA interference for sequence-specific post transcriptional gene silencing (Abstract), and further teach that their method may be used in analytic procedures, e.g. in the functional and /or phenotypical analysis of gene expression profiles and/or proteomes (paragraph [0036, column 2, p. 3). "Using RNAi based knockout technologies, the expression of an endogenous target gene may be inhibited in a target cell" (paragraph [0037], column 2, p. 3), further, "capable of inhibiting the expression of at least one endogenous target gene. "The endogenous gene may be complemented by an exogenous target nucleic acid coding for the target protein or a variant or mutated form of the target protein, e.g. a gene or a cDNA" (paragraph [0038], column 2, p. 3). Thus, the teachings of Tuschl et al. are not limited to therapeutic treatment. Applicants should further note that exogenous and endogenous target

genes described by Tuschl et al. are equivalent to specific isoforms of interest and other isoforms of a gene product not of interest, respectively, as the exogenous target nucleic acid is encoding the endogenous target protein, and hence is capable of complementation. As stated by Tuschl et al. the complementation may be achieved by an exogenous target nucleic acid coding for the endogenous gene; i.e. the endogenous and exogenous target nucleic acids have identical sequences.

Therefore, the rejection of claims 1-12 and 14-20, is maintained for reasons of record and the foregoing discussion.

Conclusion

Claims 1-12 and 14-20, are not allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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